

SFUND RECORDS CTR 44889



DEPARTMENT OF THE AIR FORCE AIR FORCE RESEARCH LABORATORY WRIGHT-PATTERSON AIR FORCE BASE OHIO 45433

27 OCT 98

MEMORANDUM FOR EPA

NCEA (MD-52) RTP, NC 27711 ATTN: Annie Jarabek

FROM: AFRL/HEST 2856 G Street

Wright-Patterson AFB OH 45344-7400

SUBJECT: Consultative Letter, AFRL-HE-WP-CL-1998-0026, Histopathology Report for Thyroids from a Fourteen-Day Oral Dosing Toxicity Study of Ammonium Perchlorate

1. Design:

Groups of six male and six female Sprague-Dawley rats were dosed with AP in drinking water at concentrations of 0 (control), 1.25, 5.0, 12.5, 25, 50, 125, or 250 mg/L (Caldwell, et al. 1995). The actual dose of AP administered to each animal was calculated by multiplying the concentration of AP administered in the drinking water by each animal's average water consumption over the 14-day period and dividing this number by each animal's average body weight over the 14-day period. Animals were sacrificed after fourteen days. Thyroids were collected and prepared for histopathological analysis.

2. Histopathology:

Histopathological analysis was performed and reported by Eggers (1996) and included as Attachment 1. Individual animal histology data is included as Attachment 2.

3. Results and Comments:

Incidence of follicular epithelial cell hypertrophy and decrease in follicular lumen size is summarized in Table 1. Changes in epithelial cells and follicular lumen size were present in all thyroids examined starting with the 25 mg/kg group. Severity of follicular epithelial cell hypertrophy and and decrease in follicular lumen size is summarized in

Table 2. The change in hypertrophy was significantly different from control at a lower dose of ammonium perchlorate (5 mg/kg) than the change in lumen area (25 mg/kg). The scoring parameters for severity are shown in Table 3. Statistical analysis reported by Eggers (1996) in his histopathology report is the combined analysis of male and female rats and documentation is not on file. It is recommended that the statistics be performed again and the documentation included in the final report.

TABLE 1. INCIDENCE OF THYROID FOLLICULAR CELL HYPERTROPHY AND DECREASE IN FOLLICULAR LUMEN SIZE IN MALE AND FEMALE RATS EXPOSED TO AMMONIUM PERCHLORATE IN DRINKING WATER FOR 14 DAYS

A. INCIDENCE OF THYROID FOLLICULAR CELL HYPERTROPHY

CONTROL	1.25	5.0	MALE 12.5	25	50	125	250
2	5	5	5	6	6 .	6	6 ·
			FEMA	LE			
CONTROL	1.25	5.0	12.5	25	50	125	250
2	1.	5	4	6	6	6	6

^{*} n=5

B. INCIDENCE OF FOLLICULAR LUMEN SIZE DECREASE

			MALI	3			
CONTROL	1.25	5.0	12.5	25	50 .	125	250
3	4	5	5	6	6	6	6
			FEMA	LE			
CONTROL	1.25	5.0	12.5	25	50	125 .	250
4	2ª	6	5	6	6	6	6

⁴ m=4

TABLE 2. SEVERITY OF THYROID FOLLICULAR CELL HYPERTROPHY AND DECREASE IN FOLLICULAR LUMEN SIZE IN MALE AND FEMALE RATS EXPOSED TO AMMONIUM PERCHLORATE IN DRINKING WATER FOR 14 DAYS

MEAN ± STANDARD DEVIATION

A. SEVERITY OF THYROID FOLLICULAR CELL HYPERTROPHY

CONTROL	1.25	5.0	MALE 12.5	E 25	50	125	250
0.67	1.67	1.83	2.0	2.67	3.0	3.67	4.0
0.94	0.75	0.9	1.15	0.94	1.0	0.75	0.0
			FEMA	LE			
CONTROL	1.25	5.0	12.5	25	50	125	250
0.67	0.40ª	1.67	1.33	2.67	2.67	3.33	4.00
0.94	0.80	0.75	0.94	0.94	0.94	0.94	0.00
* n=5							

B. SEVERITY OF FOLLICULAR LUMEN SIZE DECREASE

			MALE	į			
CONTROL	1.25	5.0	12.5	25	50	125	250
0.50	0.67	0.83	1.50	1.67	3.33	4.33	4.00
0.50	0.47	0.37	1.12	0.94	0.75	0.94	1.00
			FEMA	LE			
CONTROL	1.25	5.0	12.5	25	50	125	250
0.67	0.40ª	1.00	0.83	1.67	1.67	3.00	4.00
0.47	0.49	0.00	0.37	0.94	0.94	1.26	1.00

^{*} n=5

Table 3. Scoring parameters for severity of hypertrophy and decrease in follicular lumen size.

Normal	0
Slight	1
Mild	2
Moderate	3
Marked	4
Severe	5

4. Reference:

Caldwell, D.J., Kinkead, E.R., Narayanan, L., King, J.H. and Mattie, D.R. Results of a Fourteen Day Oral-Dosing Toxicity Study of Ammonium Perchlorate. 1995 JANNAF Safety and Environmental Protection Subcommittee. CPIA Publication 634, Vol. 1:179-184, Tampa, FL, 4-8 Dec 1995.

Eggers, J. 1996. Toxicity evaluation of ammonium perchlorate administered in the drinking water of Sprague-Dawley rats. Study A10. A Narrative Pathology Report – Pilot Study.

5. Scientific POC:

This report was prepared by David R. Mattie, PHD, in collaboration with Dr Jeffrey Eggers, pathologist. Dr Mattie can be reached at AFRL/HEST, Wright-Patterson AFB, OH (937) 255-5150, ext 3110, E-Mail: mattied@falcon.al.wpafb.af.mil

Stephen R. Channel, Maj., USAF, BSC Chief, Operational Toxicology Branch Human Effectiveness Directorate

ATTACHMENT 1.

TOXICITY EVALUATION OF AMMONIUM PERCHLORATE ADMINISTERED IN THE DRINKING WATER OF SPRAGUE-DAWLEY RATS

Study number A10 Start date 25 July, 1995 Study Director: D. Caldwell Study Pathologist: J. Eggers

NARRATIVE PATHOLOGY REPORT - PILOT STUDY

Gross observations:

At necropsy, all rats utilized in this study were in good general condition. Both edema and atrophy of the thyroid gland were diagnosed grossly in low numbers of animals from control and treatment groups, and these findings did not appear to be dose related. Thyroid enlargement was noted grossly in one high dose (250 mg/kg) female and in one mid dose (25 mg/kg) male animal.

Histopathology:

The thyroid gland was the only tissue examined histologically in this 14-day pilot study. Averages of both thyroid follicular lumen size and thyroid follicular epithelial hypertrophy were estimated using a standard microscope ocular grid as a reference for measurement. The incidence and average severity score for each finding are noted in table 1. There was no statistical difference between males and females in the incidence or dose response for either finding.

Follicular lumen size (colloid area): There was a dose-related decrease in follicular lumen size starting at the 5 mg/kg dose progressing to the 250 mg/kg (high) dose group. Follicular lumens in the 25, 50, 125, and 250 mg/kg dose groups were significantly (p<0.01) decreased in area compared to controls (Tille 2). The progressive decrease in lumen size was also statistically significant (p<0.01) between different dosage groups as follows: control through 12.5 mg/kg > 2.5 mg/kg > 50 mg/kg > 125 and 250 mg/kg.

Follicular epithelial cell hypertrophy: A significant (p<0.01) dose-related increase in severity of follicular cell hypertrophy was observed in the all except the lowest (1.25 mg/kg) dose group as compared to controls. The progressive increase in follicular cell hypertrophy was also statistically significant (p<0.01) between different dosage groups as follows: Control and 1.25 mg/kg < 5 and 12.5 mg/kg < 25 and 50 mg/kg < 125 and 250 mg/kg (T L 2).

Morphometry: Computerized morphometric image analysis of follicular lumen size was performed on 5 dose groups (Controls, 1.25 mg/kg, 12.5 mg/kg, 50 mg/kg, 250 mg/kg). A statistically significant (p<0.01) decrease in lumen size was evident in 12.5, 50, and 250 mg/kg dose groups in male rats and in 50 and 250 mg/kg dose groups in female rats compared to controls.

Discussion:

Although there was no statistical difference in severity between males and females for the histomorphologic changes, in general, male rats appeared more sensitive to perchlorate effects on the thyroid at most dose levels. This was also true of thyroid follicular lumen area as measured by morphometry.

The thyroid gland is considered a target organ of perchlorate toxicity. The pathogenesis of perchlorates effect on the thyroid is thought to be through inhibition of I uptake by the gland resulting in decreased levels of circulating T3 and T4 hormones. The morphologic changes in the thyroid follicles observed in this study are most likely due to a change in thyroid follicular epithelium function in response to increasing TSH levels secondary to decreasing T3 and T4 hormones. Therefore, the best parameter to determine a no observed adverse effect level (NOEL) for perchlorate in relation to rat thyroid gland function may be the maximum dose that does not significantly increase TSH levels in these animals.

Jeffrey S. Eggers MAJ, VC, USA Chief, AMRU
3 Fel 96

8828088888 8882888888 888888888	22222222222222222222222222222222222222	2222222	Armstr	ong Lab	oratory	Toxi	cology Div	ision WPAFB OF	222222222	22222222222222
NOTE: PRINTED	FOR : JEFF EGGERS		(A)						Ti	able 1
	·		PPPP	AAA	TTTTT	H	H TTTTT	000 X X		•
			P P	A A		н	H T	o o x x	•	•
			P P	λλ	_	H	н т	0 0 X X		··
			PPPP	λλ		нин		0 0 X		C
			P	AAAAA		Ħ	H T	0 0 X X		20110
			P	λ λ		H	н т	0 0 X X		- u ve
			P	A A		H	H T	000 X X		
		•								
	•	PPFFFFFFFF		0000	RRRRRR		000000	000000	333333	•
		PPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPP	,00	0000	RRRRRR	RR	000000	000000	333333	
		PF	00	00	RR	RR	00 0		33 33	
		PF	00	00	RR	RR	00 0		33 33	
		PF	00	00	RR	RR	00 000		. 33	
		PP	00	00	RR	RR	00 000		. 33	
		FFFFFFF	00	00	RRRRRR		00 00 0		33	•
		PPPPPPPP	00	00	RRRRRR		00 00 0		33	
		PF	00	00	RR RR		0000 0		33 33	
		PF PF	00 00	00 00		RR	0000 0		33 33	
		rr PP	. 00	. 00		RR	00 0		33 33	
		rr Pr		0000	RR	RR	000000	000000	333333	
		?		0000	RR	RR	000000	000000	333333	
				-	4.4.	****	***************************************	***************************************		
			DDDD	DDDD	аааа		TTTTTTTTT		555555555	
			DDDD	DDDD	λλλλ	λλ	TTTTTTTTT	T ;;;	555555555	
			DD	DD	λλ	λA	TT	;;;;	55	
			DD	DD	AA	λA	TT	;;;;	55	
	•		DD	DD	AA	λλ	TT		555555	
•			DD	DD	λλ	AA	TT		555555	
			DD	DD	λλ	λλ	TT	;;;;	55	
			DD	DD	λλ	AA	TT	;;;;	55	•
			DD	DD	ΧΑΛΑΑΑ		TT	;;;;	55	
			DD	DD	λλλλλλ		TT	;;;;	55	
		• • • •	DD	DD	ΥΥ	AA	TT	;;	55 55 55 55	
		• • • •	DD DDDD	DD	AA AA	λλ	TT TT	;;	555555	
		• • • •			λλ	λλ	TT	;;	555555	
			טטטט	DDDD	AA.	~~	TT	i i	フラフママン	

ввввввввв

ввввввввв

BBBBBBBBBB

File RAVEN\$DUA3:{PATHTOX.RUN.P]FOR003.DAT;5 (7668,10,0), last revised on 3-FEB-1996 11:31, is a 34 block sequential file owned by UIC {XT,PATHTOX}. The records are variable length with FORTRAN (FTN) carriage control. The longest record is 132 bytes.

Job FOR003 (289) queued to SYS\$LASER2 on 3-FEB-1996 11:31 by user PATHTOX, UIC [XY,PATHTOX], under account XY at priority 100, started on printer LTA3: on 3-FEB-1996 11:31 from queue SYS\$LASER2.

BBBBBBBBB	22222222 2222222222222222222222222222	888888888
BBBBBBBBBB	22222222222222222222222222222222222222	888888888
888888888	222222222222222222222222222222222222222	BBBBBBBBB

Incidence Summary of Microscopic Observations Study number: aprfl

All Diagnoses
Study start date: 25-Jul-95

PRINTED: 03-Feb-96

Page: 1

ORAL UPTAKE/REPEATED DOSE GAVAGE

KAT/F 344	. Scudy stat	t date	. 25-5 q	1-93		URA	C OLIVE	D/KEPEA	IED DOSE	, GAVAGE
Notes: Animals = all dead animals				- A n i	m a 1	s λ	f f •	c t • d		
Controls from group(s): 1	Animal sex:				H	a l e s				
Dosing units: (mg/kg)	Group dosage level:	Ctls	1.2500	5.0000	12.500	25.000	50.000	*****	*****	
Tissues With Diagnoses	No. in group:	6	6	6	6	6	6	6	6	
THYROID	Number examined:	6	6	6	6	6	6	6	6	
follicular cell hypertrophy/hyperplasia		2	5	5					-6	
follicular lumen size (decreasing colloid	area)1	3	4	5	5	6	-6	-6	-6	

Note: Entries flagged with a - (minus) are significantly different from control at the 0.05 level using the Kolmogorov-Smirnov two tailed test.

Incidence Summary of Microscopic Observations Study number: aprf1

All Diagnoses
Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

PRINTED: 03-Peb-96

Page: 2

Notes: Animals = all dead animals			- A n i		 l s	 A	t t • ·	c t • d		
Controls from group(s): 1 Anima	al sex:			P	• #	1 4				
Dosing units: (mg/kg) Group dosage									*****	
Tissues With Diagnoses No.in	group: 6	6		6 	6	6	6	6		
THYROID	amined: 6	5		 5	6	6	6	6	6	
follicular cell hypertrophy/hyperplasia	2	1	5	5	4	6	6	6	-6	
follicular lumen size (decreasing colloid area)1	4	2	6	5	5	6	6	-6	-6	

Note: Entries flagged with a - (minus) are significantly different from control at the 0.05 level using the Kolmogorov-Smirnov two tailed test.

TOXICOLOGY DIVISION		
ARMSTRONG LABORATORY		
WRIGHT-PATTERSON AFB,	OH	45433
DAT /# 344		

Summary Table of Microscopic Observations With Average Severity Grade Study number: aprfl

Nonneoplastic Graded Diagnoses

Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

PRINTED: 03-Feb-96

Page: 1

tes: Animals = all dead animals			- Ani	mal:	5 λ	ffe	: t • d	
ontrols from group(s): 1 Animal sex:				M	1 1 • s			
osing units: (mg/kg) Group dosage level:	Ctls	1.2500	5.0000	12.500	25.000	50.000	*****	*****
issues With Diagnoses No. in group:	6	6	6	6	6	6	6	6
HYROID	 6	6	6	 6	6	 6	6	6
follicular cell hypertrophy/hyperplasia	2	5	5	5	6	6	6	6
Average severity:	0.7	1.7	2.0	2.0	2.7	3.0	3.7	4.0
follicular lumen size (decreasing colloid area)1	3	4	5	5	6	6	6	6
Average severity:	0.5	0.7	0.8	1.5	1.7	3.3	4.3	4.0

TOXICOLOGY DIVISI	CON		
ARMSTRONG LABORAT	CORY		
WRIGHT-PATTERSON	AFB,	OH	45433
RAT/F 344	-		

Summary Table of Microscopic Observations With Average Severity Grade Study number: aprfl Nonneoplastic Graded Diagnoses Study start date: 25-Jul-95 ORAL UPT

ORAL UPTAKE/REPEATED DOSE, GAVAGE

PRINTED: 03-Feb-96 Page: 2

,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,								.,	
Notes: Animals = all dead animals .				Ani	mals	λ	f f • c	t • d	
Controls from group(s): 1	Animal sex:			-	F • 1	. a 1 .	s		
Dosing units: (mg/kg)	Group dosage level:	Ctls	1.2500	5.0000	12.500	25.000	50.000		*****
Pissues With Diagnoses	No. in group:	6	6	6	6	6	6	6	6
THYROID	Number examined:	6	5	6	6	6	6	6	6
follicular cell hypertrophy/hyperplasia		2	1	5	4	6	6	6	6
	Average severity:	0.7	0.4	1.7	1.3	2.7	2.7	3.3	4.0
follicular lumen size (decreasing colloid	area)1	4	2	6	5	6	6	. 6	6
	Average severity:		0.4				1.7		

Individual Animal Report of Gross and Microscopic Diagnoses

Study number: aprfl

Tissues With Gross Observations Only

Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

Animal: 22

Sex: Male

Group: 8

Dose level: 250.000 (mg/kg)

Terminal body weight (kgs): 0.43

Day of death: 15 Status: Final sacrifice

PRINTED: 03-Feb-96

Page: 1

Tissue

Gross observations / Comments

Individual Animal Report of Gross and Microscopic Diagnoses

Study number: aprf1

Tissues With Gross Observations Only Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

PRINTED: 03-Feb-96

Page: 2

Animal: 10

Sex: Male

Gross observations / Comments

Group: 8

Day of death: 14 Status: Fin

Dose level: 250.000 (mg/kg)

Tissue

Status: Final sacrifice

Terminal body weight (kgs): 0.59

Individual Animal Report of Gross and Microscopic Diagnoses

Study number: aprf1

Tissues With Gross Observations Only

Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

Animal: 23

Sex: Male

Group: 8

Dose level: 250.000 (mg/kg)

Day of death: 15

Status: Final sacrifice

Terminal body weight (kgs): 0.49

PRINTED: 03-Feb-96

Page: 3

Gross observations / Comments

Individual Animal Report of Gross and Microscopic Diagnoses

Study number: aprf1

Tissues With Gross Observations Only

Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

PRINTED: 03-Feb-96

Page: 4

Animal: 3

Sex: Male

Gross observations / Comments

Group: 8

Dose level: 250.000 (mg/kg)

Day of death: 14

Status: Final sacrifice

Terminal body weight (kgs): 0.55

Tissue

Microscopic observations / Comments

THYROID ENLARGED/

follicular cell hypertrophy/hyperplasia, Marked.

follicular lumen size (decreasing colloid area)1, Severe.

Individual Animal Report of Gross and Microscopic Diagnoses

Study number: aprf1

Tissues With Gross Observations Only Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

PRINTED: 03-Fab-96

Page: 5

Animal: 37

Sex: Male

Group: 8

Dose level: 250.000 (mg/kg)

Day of death: 15 Status: Final sacrifice

Terminal body weight (kgs): 0.49

Tissue

Gross observations / Comments

THYROID EDEMA/

Individual Animal Report of Gross and Microscopic Diagnoses

Study number: aprf1

Tissues With Gross Observations Only

Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

PRINTED: 03-Feb-96

Page: 6

Animal: 18

Sex: Male

Group: 8

Dose level: 250.000 (mg/kg)

Day of death: 14

Status: Final sacrifice

Terminal body weight (kgs): 0.54

Gross observations / Comments

Microscopic observations / Comments

follicular cell hypertrophy/hyperplasia, Marked.

follicular lumen size (decreasing colloid area)1,

Moderate.

Special Histological Comments on Tissues Study number: aprfl

PRINTED: 02-Feb-96 Page: 1

Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

Animal Number			Date and Data was e		Oper.	Tissue	Special histological comment
55	7	2/1	10-0ct-95	10:53	88	THYROID	thyroid lost in processing
59	F	5/1	10-Oct-95	10:57	8.8	THYROID	ultimobranchial cyst
80	F	5/1	10-0ct-95	10:58	8.8	THYROID	ultimobranchial cyst

·	111 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	: # 1
<u> </u>	
	::
•	
	## <u>#</u>
	·
	:
dos - remones.	· · · · · · · · · · · · · · · · · · ·
The sate of the onimal did not affect the	
underlined means that the groups are the same	
28D	
0	·
Digulicant at 1-0.01	
Spir 1.1 1.50 3.50 3.67 4.00 Euman size	3 6,58 6.
oundersphi / phortrophi 00.4 02.E E8.2 13.5 12.1 E8.1 PO.	
058 21 02 24 251 25 25	1 Joseph)

Talke 2. Histo statistics

Animal: 24 Day of death: 14 S	Sex: Male	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
	GOOD/ ,NGL - PP		
••		YROID	

Animal: 3 Day of death: 1	9 Sex: Male 5 Study/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obs	ervations / Comments
GEN CONDITION	. GOOD/ ,ngl-jwn		
The following t	issues are examined/unremarkable	THYROID	

	·						
Animal: 11	Sex: Male	Group: 1	Dose level: 0.0000 (mg/kg)				
Day of death: 14 Study	Day of death: 14 Study/dosing phase						
Tissue Gr	ross observations / Comments		Microscopic observations / Comments				
THYROID E	DEMA/ ,SLIGHT SWELLING AROUND THYROIDS - PP		follicular lumen size (decreasing colloid area)1,				

Animal: 15 Day of death: 14 S	Sex: Male tudy/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue Gross observations / Comments		Microscopic obs	servations / Comments
THYROID	. No gross observed on tissue.	follicular cel	hypertrophy/hyperplasia, Mild.
		follicular lume Slight.	en size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: 47 Day of death: 15	Sex: Male Study/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)	
Tissue	Gross observations / Comments	Microscopic observations / Comments		
THYROID	. No gross observed on tissue.	follicular cel	l hypertrophy/hyperplasia, Mild.	
GEN CONDITION	. GOOD/ ,ngl-jwn			

Animal: 44 Sex: Male Group: 1 Dose level: 0.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue Gross observations / Comments Microscopic observations / Comments

THYROID No gross observed on tissue. follicular lumen size (decreasing colloid area)1, Slight.

GEN CONDITION . . . GOOD/ ,ngl-jwn

Animal: Day of death:	12 Sex: Male 14 Study/dosing phase	Group: 2	Dose level: 1.2500 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
THYROID	No gross observed on tissue.	follicular lum Slight.	en size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

Animal: 14 Sex: Male Day of death: 14 Study/dosing phase		Group: 2	Dose level: 1.2500 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obse	ervations / Comments
THYROID	EDEMA/ ,AROUND THYROIDS - PP	follicular cell	hypertrophy/hyperplasia, Mild.

Animal: 27 Day of death: 15 St	Sex: Male cudy/dosing phase	Group: 2	Dose level: 1.2500 (mg/kg)			
Tissue Gross observations / Comments		Microscopic observations / Comments				
THYROID	. No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild.				
		follicular lu Slight.	men size (decreasing colloid area)1,			

GEN CONDITION . . . GOOD/ ,NGL-JWN

Animal: 25 Sex: Male Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue Gross observations / Comments Microscopic observations / Comments

THYROID No gross observed on tissue. follicular cell hypertrophy/hyperplasia, Mild.

follicular lumen size (decreasing colloid area)1, Slight.

GEN CONDITION . . . GOOD/ ,ngl-jwn

Group: 2 Dose level: 1.2500 (mg/kg) Animal: 19 Sex: Male

Day of death: 15 Study/dosing phase

Gross observations / Comments Microscopic observations / Comments

follicular cell hypertrophy/hyperplasia, Mild. THYROID No gross observed on tissue.

follicular lumen size (decreasing colloid area)1,

Slight.

GEN CONDITION . . . GOOD/ ,ngl-jwn

!					***************************************					
•	Animal: 1	Sex: Male	Group: 2		Dose	level:	1.2500	(mg/kg)		
	Day of death: 14 Study/dosing phase									
	Tissue	Gross observations / Comments		Microscopic observation	s / (Comments				
1	THYROID	. atrophy/ LEFT IS ATROPHIED - PP		follicular cell hypertr	ophy	/hyperpl	asia, Mi	.ld.		

Animal: 13 Day of death: 14 S	Sex: Male tudy/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments		Microscopic observations / Comments
THYROID	. EDEMA/ ,MILD SWELLING AROUND THYROIDS - PP	PP follicular cell hypertrophy/hyperplasia, Marke	
			follicular lumen size (decreasing colloid area)1,

Animal: 9 Day of death: 14	Sex: Male Study/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic observations / Comments	
THYROID	. EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular	cell hypertrophy/hyperplasia, Mild.
, ,		follicular l	lumen size (decreasing colloid area)1,

Animal: 4		Group: 3	Dose level: 5.0000 (mg/kg)
Day of death:	15 Study/dosing phase		<u></u>
Tissue	Gross observations / Comments	Microscopic observations / Comments	
THYROID No gross observed on tissue.		follicular cell hypertrophy/hyperplasia, Mild.	
		follicular	lumen size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,ngl-jwn

Animal: 42 Day of death: 15	Sex: Male Study/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obse	ervations / Comments
THYROID	. No gross observed on tissue.	follicular cell	hypertrophy/hyperplasia, Mild.
		follicular lumen Slight.	n size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,ngl-jwn

Animal: Day of death:	29 Sex: Male 15 Study/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obs	servations / Comments
GEN CONDITION	GOOD/ ,ngl~jwn		
The following microscopical:	tissues are examined/unremarkable ly:	THYROID	

Animal: 2	Sex: Male Study/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obs	ervations / Comments
THYROID	No gross observed on tissue.	follicular cell	hypertrophy/hyperplasia, Mild.
		follicular lume Slight.	n size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: 41 Day of death: 15	Sex: Male Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
THYROID	. No gross observed on tissue.	follicular cel	l hypertrophy/hyperplasia, Marked.
		follicular lum Moderate	men size (decreasing colloid area)1,

Animal: 17 Day of death: 14 9	Sex: Male Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ol	oservations / Comments
THYROID	. No gross observed on tissue.	follicular ce	ll hypertrophy/hyperplasia, Mild.
		follicular lum Moderate.	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: Day of death:	38 Sex: Male 15 Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obse	rvations / Comments
THYROID	No gross observed on tissue.	follicular cell	hypertrophy/hyperplasia, Mild.

Animal: 26 Day of death: 14 S	Sex: Male Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	. EDEMA/ ,around and under thyroids -pp	follicular Slight.	lumen size (decreasing colloid area)1,

Animal: 20 Day of death: 14	Sex: Male Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	No gross observed on tissue.	follicular c	ell hypertrophy/hyperplasia, Mild.
		follicular l Slight.	umen size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: Day of death:	45 Sex: Male 15 Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
	No gross observed on tissue.	follicular cei	n,pertrophy/hyperplasia, Mild.
		follicular lum Slight.	en size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL-JWN

Animal: 30 Day of death: 15 S	Sex: Male tudy/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	observations / Comments
THYROID	. No gross observed on tissue.	follicular ce	ell hypertrophy/hyperplasia, Mild.
	· .	follicular lu Slight.	umen size (decreasing colloid area)1,

Animal: 16 Day of death: 14 S	Sex: Male study/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	. atrophy/ ,LEFT SIDE - PP	follicular	cell hypertrophy/hyperplasia, Marked.
		follicular : Moderate.	lumen size (decreasing colloid area)1,

Animal: 7 Day of death: 14 S	Sex: Male Study/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	bservations / Comments
THYROID	. EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular ce	ll hypertrophy/hyperplasia, Marked.
		follicular lu Slight.	men size (decreasing colloid area)1,

Animal: 36 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 15 Study/dosing phase

sue Gross observations / Comments

Microscopic observations / Comments

THYROID No gross observed on tissue.

follicular cell hypertrophy/hyperplasia, Mild.

follicular lumen size (decreasing colloid area)1, Slight.

Animal: 4 Day of death: 14	Sex: Male Study/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic of	bservations / Comments
THYROID	atrophy/ ,SLIGHT AROUND THYROIDS - PP	follicular ce	ll hypertrophy/hyperplasia, Mild.
	atrophy/ ,RIGHT SMALLER	follicular lu	men size (decreasing colloid area)1,

Animal: 43 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue Gross observations / Comments Microscopic observations / Comments

THYROID No gross observed on tissue. follicular cell hypertrophy/hyperplasia, Mild.

follicular lumen size (decreasing colloid area)1, Slight.

GEN CONDITION . . . GOOD/ , NGL-JWN

Animal: 33 Day of death: 14 S	Sex: Male tudy/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments		Microscopic observations / Comments
HYROID	. atrophy/ ,left,slightly,edema around thyroid	- PP	follicular cell hypertrophy/hyperplasia, Mild.
			follicular lumen size (decreasing colloid area)1, Moderate.

Animal: 46 Day of death: 15 S	Sex: Male tudy/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	. No gross observed on tissue.	follicular c	ell hypertrophy/hyperplasia, Marked.
		follicular 1	umen size (decreasing colloid area)1,

Animal: 8 Day of death: 14	Sex: Male Study/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	bservations / Comments
THYROID	. No gross observed on tissue.	follicular ce	ll hypertrophy/hyperplasia, Mild.
		follicular lu Moderate.	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

	·		
Animal: 6 Day of death: 14 S	Sex: Male Study/dosing phase	Group: 6	Dose leve_: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	. atrophy/ ,LEFT SIDE - PP	follicular o	ell hypertrophy/hyperplasia, Mild.
		follicular l Moderate.	umen size (decreasing colloid area)1,

Animal: 34 Day of death: 15 St	Sex: Male udy/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	No gross observed on tissue.	follicular	cell hypertrophy/hyperplasia, Marked.
		follicular .	lumen size (decreasing colloid area)1,

Animal: 40 Day of death: 15 S	Sex: Male tudy/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopio	c observations / Comments
THYROID	. No gross observed on tissue.	follicular	cell hypertrophy/hyperplasia, Marked.
		follicular Moderate.	lumen size (decreasing colloid area)1,

Animal: 28 Day of death: 14 S	Sex: Male tudy/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue Gross observations / Comments		Microscopio	c observations / Comments
THYROID No gross observed on tissue.		follicular	cell hypertrophy/hyperplasia, Marked.
		follicular Severe.	lumen size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

Animal: 2 Day of death: 14	Sex: Male Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID No gross observed on tissue.		follicular o	cell hypertrophy/hyperplasia, Mild.
		follicular l Moderate.	lumen size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: : Day of death: :	Sex: Male Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obse	ervations / Comments
THYROID	No gross observed on tissue.	follicular cell	hypertrophy/hyperplasia, Marked.

follicular lumen size (decreasing colloid area) 1, Moderate.

Animal: 35	Sex: Male	Group: 7	Dose level: 125.000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue Gross observations / Comments Microscopic observations / Comments

THYROID No gross observed on tissue. follicular cell hypertrophy/hyperplasia, Marked.

follicular lumen size (decreasing colloid area)1, Severe.

Animal: 31 Day of death: 15 S	Sex: Male	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
THYROID	. No gross observed on tissue.	follicular cel	l hypertrophy/hyperplasia, Marked.
	•	follicular lum	en size (decreasing colloid area)1,

Severe.

Animal: 5 Day of death: 14	Sex: Male Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID atrophy/ ,LEFT - PP		follicular o	cell hypertrophy/hyperplasia, Marked.
•		follicular l Severe.	lumen size (decreasing colloid area)1,

Animal: 22 Day of death: 15 Study/do	Sex: Male osing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue Gross	observations / Comments	Microscopic	observations / Comments
THYROID No gr	coss observed on tissue.	follicular c	ell hypertrophy/hyperplasia, Marked.
		follicular l	umen size (decreasing colloid area)1,

Animal: 10 Day of death: 14	Sex: Male Study/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
THYROID No gross observed on tissue.		follicular cel	l hypertrophy/hyperplasia, Marked.
		follicular lum Moderate.	en size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

Animal Day of death	: 23 Sex: Male : 15 Study/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopio	cobservations / Comments
THYROID	No gross observed on tissue.	follicular	cell hypertrophy/hyperplasia, Marked.

Moderate.

follicular lumen size (decreasing colloid area) 1,

GEN CONDITION . . . GOOD/ , NGL-JWN

Animal: 3 Day of death: 14 S	Sex: Male tudy/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments		Microscopic observations / Comments
THYROID	. ENLARGED/ ,RIGHT ENLARGED 2X AND DARK BROWN	- PP	follicular cell hypertrophy/hyperplasia, Marked.
			follicular lumen size (decreasing colloid area)1, Severe.

Animal: 37 Day of death: 15 S	Sex: Male Study/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	. No gross observed on tissue.	follicular o	ell hypertrophy/hyperplasia, Marked.
		follicular l Severe.	umen size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL-JWN

Animal: 18	Sex: Male	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Study/dosing phaseGross observations / Comments	Microscopi	c observations / Comments
THYROID	. EDEMA/ ,AROUND THYROID - PP	follicular	cell hypertrophy/hyperplasia, Marked.
•		follicular Moderate.	lumen size (decreasing colloid area)1,

Animal: 86 Day of death: 14 S	Sex: Female tudy/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic observati	Lons / Comments
THYROID	. No gross observed on tissue.	follicular lumen size Slight.	e (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

Animal: 68 Day of death: 14 S	Sex: Female Study/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic of	oservations / Comments
THYROID No gross observed on tissue.		follicular cel	ll hypertrophy/hyperplasia, Mild.
		follicular lum Slight.	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

							
	00 Sex: 5 Study/dosing phase	Female	Group: 1		Dose level:	0.0000	(mg/kg)
Tissue	Gross observation	s / Comments		Microscopic observation	ns / Comments		
GEN CONDITION .	GOOD/ ,NGL-JWN						
The following t microscopically	issues are examined/un	remarkable 1	rhyroid				

Animal: 90 Day of death: 15 St	Sex: Female cudy/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	observations / Comments
THYROID	No gross observed on tissue.	follicular lu Slight.	umen size (decreasing colloid area)1,

Animal: 71 Day of death: 14 S	Sex: Female tudy/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	bservations / Comments
THYROID	. No gross observed on tissue.	follicular ce	ll hypertrophy/hyperplasia, Mild.
		follicular lu Slight.	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: Day of death:	95 Sex: Female 15 Study/dosing phase	Group: 1	Dose level: 0.0000 (mg/kg)
Tissue	Gross observations / Comment	s .	Microscopic observations / Comments
	GOOD/ ,NGL-JWN		
	tissues are examined/unremarkable	THYROID	

Animal:	73 Sex: Female	Group: 2	Dose level: 1.2500 (mg/kg)
Day of death:	15 Study/dosing phase		
Tissue	Gross observations / Comments	Microscopic obse	ervations / Comments
THYROID	No gross observed on tissue.	follicular lume: Slight.	n size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL-JWN

	al: 58 Sex: th: 14 Study/dosing phase	Female	Group: 2	Dose level: 1.2500 (mg/kg)
Tissue	Gross observation	s / Comments	Microscopic observat	ions / Comments
THYROID	No gross observed	on tissue.	follicular lumen siz	e (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

Animal: 67 Sex: Female Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 15 Study/dosing phase

bay of death. 15 beday, dobting phase

Tissue Gross observations / Comments

Microscopic observations / Comments

THYROID No gross observed on tissue.

follicular cell hypertrophy/hyperplasia, Mild.

Animal: 51 Day of death: 14	Sex: Study/dosing phase	Female	Group: 2	Dose level: 1.2500 (mg/k	.g)
Tissue	Gross observation	s / Comments	Microscop	pic observations / Comments	
GEN CONDITION .	GOOD/ ,NGL - PP				
The following ti	ssues are examined/un	remarkable THYROID			

Animal: 55 Day of death: 14 St	Sex: Female udy/dosing phase	Group: 2	Dose level: 1.2500 (mg/kg)
Tissue	Gross observations / Comments		Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT SWELLING BETWEEN THYROID PP	AND TRACHEA -	Tissue is missing.

/ thyroid lost in processing

=	Study/dosing phase	Group: 2	Dose level: 1.2500 (mg/kg)
Tissue	Gross observations / Comments	· ·	observations / Comments
GEN CONDITION	GOOD/ ,NGL-JWN		
The following ti	ssues are examined/unremarkable	THYROID	

_			.
Animal: Day of death:	63 Sex: Female 14 Study/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obs	servations / Comments
THYROID	No gross observed on tissue.	follicular cell	hypertrophy/hyperplasia, Mild.
		follicular lume Slight.	en size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: 69 Day of death: 15 S	Sex: Female tudy/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obs	ervations / Comments
THYROID	. No gross observed on tissue.	follicular cell	hypertrophy/hyperplasia, Mild.

follicular lumen size (decreasing colloid area)1, Slight.

Animal: 91 Day of death: 15 S	Sex: Female tudy/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic of	oservations / Comments
THYROID No gross observed on tissue.		follicular cel	l hypertrophy/hyperplasia, Mild.
		follicular lum Slight.	men size (decreasing colloid area)1,

Animal: 88 Sex: Female Group: 3 Dose level: 5.0000 (mg/kg)

Day of death: 15 Study/dosing phase

.....

Tissue Gross observations / Comments Microscopic observations / Comments

THYROID No gross observed on tissue. follicular cell hypertrophy/hyperplasia, Mild.

follicular lumen size (decreasing colloid area)1, Slight.

Animal: 56 Day of death: 14	Sex: Female Study/dosing phase	Group: 3	Dose level: 5.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopio	c observations / Comments
THYROID	. EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular	cell hypertrophy/hyperplasia, Mild.
		follicular Slight.	lumen size (decreasing colloid area)1,

Animal: 53 Day of death: 14	Sex: Study/dosing phase	Female	Group: 3		Dose	level:	5.0000	(mg/kg)
Tissue	Gross observation	s / Comments		Microscopic observatio	ns /	Comments		
THYROID	. No gross observed	on tissue.		follicular lumen size Slight.	(decr	easing c	olloid a	area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

Animal: 99 Day of death: 15	Sex: Female Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic obs	servations / Comments
THYROID	. No gross observed on tissue.	follicular cel	hypertrophy/hyperplasia, Mild.
		follicular lume	en size (decreasing colloid area)1,

Day of death: 15 Study/dos:		Group: 4	Dose level: 12.5000 (mg/kg)
	observations / Comments		bservations / Comments
GEN CONDITION GOOD/	ngl-jwn		
The following tissues are			

microscopically:

Animal: 66 Day of death: 14	Sex: Female Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	No gross observed on tissue.	follicular o	cell hypertrophy/hyperplasia, Mild.
		follicular] Slight.	lumen size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal Day of death	: 70 Sex: Female : 14 Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic observations / Comments	
THYROID	No gross observed on tissue.	follicular lumen Slight.	size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

Animal: Day of death:	92 Sex: Female 15 Study/doming phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	oservations / Comments
THYROID No groun observed on tinnue. follicular cell hyportrop		ll hyportrophy/hyperplania, Mild.	
		follicular lu Slight.	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL-JWN

Animal: 60 Day of death: 14	Sex: Female Study/dosing phase	Group: 4	Dose level: 12.5000 (mg/kg)
Tissue	Gross observations / Comments	Microscopi	c observations / Comments
THYROID No gross observed on tissue.		follicular	cell hypertrophy/hyperplasia, Mild.
		follicular Slight.	lumen size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: 87	Sex: Study/dosing phase	Female	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue	Gross observations	/ Comments	Microscopic observ	ations / Comments
THYROID No gross observed on tissue.		follicular cell hy	pertrophy/hyperplasia, Marked.	
		•	follicular lumen s Moderate.	ize (decreasing colloid area)1,

	imal: 80 Sex: Female eath: 15 Study/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg)	
Tissue	Gross observations / Comments	Microscopic ol	oservations / Comments	
THYROID No gross observed on tissue.		follicular ce	follicular cell hypertrophy/hyperplasia, Mild.	
		follicular lun Slight.	men size (decreasing colloid area)1;	
	•	/ ultimohrand	nial ovet	

Animal: 59 Day of death: 14 S	Sex: Female Study/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg
Tissue	Gross observations / Comments	Microscopic (observations / Comments
THYROID	. No gross observed on tissue.	follicular c	ell hypertrophy/hyperplasia, Marked.
		follicular le Slight.	nmen size (decreasing colloid area)1,
		/ ultimobran	chial cyst

Animal: 94 Day of death: 15	Sex: Female Study/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
THYROID	. No gross observed on tissue.	follicular cel	l hypertrophy/hyperplasia, Mild.
		follicular lum Slight.	men size (decreasing colloid area)1,

	`		
-	76 Sex: Female 14 Study/dosing phase	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	bservations / Comments
THYROID No gross observed on tissue.		follicular cell hypertrophy/hyperplasia, Mild.	
		follicular lu Moderate.	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: 64 Day of death: 14 Study/do	Sex: Female osing phase	Group: 5	Dose level: 25.0000 (mg/kg)
Tissue Gross	observations / Comments	Microscopic obse	ervations / Comments
THYROID EDEMA	A/ ,SLIGHT AROUND THYROIDS - PP	follicular cell	hypertrophy/hyperplasia, Mild.
		follicular lumen	size (decreasing colloid area)1,

Animal: 96 Day of death: 15	Sex: Female Study/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic ob	servations / Comments
THYROID No gross observed on tissue.		follicular cel	l hypertrophy/hyperplasia, Marked.
		follicular lum Moderate.	en size (decreasing colloid area)1,

Animal: 62 Sex: Female Group: 6 Dose level: 50.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue Gross observations / Comments Microscopic observations / Comments

THYROID No gross observed on tissue. follicular cell hypertrophy/hyperplasia, Mild.

follicular lumen size (decreasing colloid area)1, Slight.

Animal: 61 Day of death: 14 S	Sex: Female Study/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic	observations / Comments
THYROID	. No gross observed on tissue.	follicular o	cell hypertrophy/hyperplasia, Marked.
e e e		follicular l Moderate.	umen size (decreasing colloid area)1,

GEN CONDITION GOOD/ , NGL - PP

Animal: 85 Day of death: 15 S	Sex: Female tudy/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	observations / Comments
THYROID	. No gross observed on tissue.	follicular ce	all hypertrophy/hyperplasia, Mild.
•		follicular lu Slight.	mmen size (decreasing colloid area)1,

Animal: 52 Day of death: 14 S	Sex: Female tudy/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	observations / Comments
THYROID	. EDEMA/ ,SLIGHTLYLAROUND THYROIDS - PP	follicular ce	ell hypertrophy/hyperplasia, Mild.
:		follicular lu Slight.	nmen size (decreasing colloid area)1,

Animal: 57 Day of death: 14 S	Sex: Female Study/dosing phase	Group: 6	Dose level: 50.0000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic of	oservations / Comments
THYROID	. No gross observed on tissue.	follicular ce	ll hypertrophy/hyperplasia, Mild.
		follicular lu Slight	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: 9	Sex: Female Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	observations / Comments
THYROID	No gross observed on tissue.	follicular ce	ell hypertrophy/hyperplasia, Mild.
		follicular lu Severe.	mmen size (decreasing colloid area)1,

Animal: 82 Day of death: 15	Sex: Female Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	observations / Comments
THYROID	. No gross observed on tissue.	follicular co	ell hypertrophy/hyperplasia, Marked.
		follicular lu	umen size (decreasing colloid area)1,

Animal: 81 Day of death: 15 9	Sex: Female Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	observations / Comments
THYROID	. No gross observed on tissue.	follicular ce	ell hypertrophy/hyperplasia, Marked.
		follicular lu Moderate.	umen size (decreasing colloid area)1,

Animal: 78 Day of death: 14 S	Sex: Female Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	bservations / Comments
THYROID	No gross observed on tissue.	follicular ce	ll hypertrophy/hyperplasia, Marked.
		follicular lu Moderate	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ , NGL - PP

•			·
Animal: 65 Day of death: 14	Sex: Female Study/dosing phase	Group: 7	Dose level: 125.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopio	c observations / Comments
THYROID	EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular	cell hypertrophy/hyperplasia, Mild.
		follicular Slight.	lumen size (decreasing colloid area)1,

Tissue	Gross observation	s / Comments		Microscopic observations	/ Cor	mments		
Animal: Day of death:	14 Study/dosing phase	Female	Group: 7	, DO	se re	ever:	125.000	(mg/kg)
3 1 3	70 700	Nama la	Gmann - 5	7	1	1 ·	105 000	(()1

THYROID No gross observed on tissue.

follicular cell hypertrophy/hyperplasia, Marked.

follicular lumen size (decreasing colloid area)1, Moderate.

GEN CONDITION . . . GOOD/ , NGL - PP

Animal: 74 Day of death: 14 S	Sex: Female Study/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic o	bservations / Comments
THYROID	. No gross observed on tissue.	follicular ce	ell hypertrophy/hyperplasia, Marked.
		follicular lu Moderate.	men size (decreasing colloid area)1,

GEN CONDITION . . . GOOD/ ,NGL - PP

Animal: 83 Sex: Female Group: 8 Dose level: 250.000 (mg/kg)

Day of death: 15 Study/dosing phase

Gross observations / Comments Microscopic observations / Comments

THYROID No gross observed on tissue. follicular cell hypertrophy/hyperplasia, Marked.

follicular lumen size (decreasing colloid area)1, Severe.

GEN CONDITION . . . GOOD/ , NGL-JWN

Animal: 75 Day of death: 15	Sex: Female Study/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopio	observations / Comments
THYROID	No gross observed on tissue.	follicular	cell hypertrophy/hyperplasia, Marked.
		follicular Severe.	lumen size (decreasing colloid area)1,

Animal: Day of death:	89 Sex: Female 15 Study/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic observations / Comments	
THYROID	No gross observed on tissue.	follicular c	ell hypertrophy/hyperplasia, Marked.
•		follicular l	umen size (decreasing colloid area)1,

	~		
Animal: 54 Day of death: 14	Sex: Female	Group: 8	Dose level: 250.000 (mg/kg)
Tissue	Gross observations / Comments	Microscopic observations / Comments	
THYROID EDEMA/ ,SLIGHT AROUND THYROID - PP		follicular cell hypertrophy/hyperplasia, Marked.	
		follicular Severe.	lumen size (decreasing colloid area)1,

Animal: 72 Day of death: 14	Sex: Female Study/dosing phase	Group: 8	Dose level: 250.000 (mg/kg)	
Tissue	Gross observations / Comments	Microscopic obs	servations / Comments	
THYROID No gross observed on tissue.		follicular cell	follicular cell hypertrophy/hyperplasia, Marked.	
•		follicular lume	en size (decreasing colloid area)1,	

Moderate.

GEN CONDITION . . . GOOD/ ,NGL - PP